SECTION 3

INDUSTRY DESCRIPTION

3.1 Introduction

This describes the pharmaceutical manufacturing industry by presenting a summary of the data and information EPA has gathered from previous EPA rulemaking efforts along with data collected as part of this effort to develop revised effluent limitations guidelines and standards for the pharmaceutical manufacturing industry. The following topics are discussed in this section:

- 3.2 discusses EPA's data collection methods and information sources;
- 3.3 presents an overview of the industry;
- 3.4 discusses pharmaceutical manufacturing processes; and
- 3.5 discusses trends in the industry.

3.2 Data Collection Methodology and Information Sources

In the course of developing effluent limitations guidelines and standards for the pharmaceutical manufacturing industry, EPA gathered and evaluated technical data from various sources to create an industry profile with respect to manufacturing processes, geographical distribution of facilities, and wastewater generation, treatment, and disposal. These data have also been used to characterize the pharmaceutical manufacturing industry's wastewater by evaluating the industry's water use, type of wastewater discharge, and occurrence of conventional, priority, and nonconventional pollutants in the wastewater. This summarizes the data collection efforts undertaken by EPA from 1975 to the present.

EPA announced it would collect additional information on this industry by publishing a Federal Register Notice (50 FR 36638, September 9, 1985) indicating its intent to reconsider whether or not to regulate methylene chloride and other volatile priority pollutants. In that Notice, EPA declared it had received new information indicating methylene chloride causes cancer in animals, such that the effects of methylene chloride discharges from pharmaceutical manufacturing plants may be more harmful than previously believed. Additionally, the results of the 1986 Domestic Sewage Study (DSS) (1) identified pharmaceutical manufacturing facilities as a significant source of organic pollutants, and found that discharges of organic compounds from these facilities are largely unregulated. Based on these data, EPA ranked this industry relatively high with respect to other industries in EPA's 304(m) plan due to environmental need (volatile organic discharges) and utility to permits and pretreatment programs. Because of the DSS findings, EPA decided to expand its review beyond priority pollutants to include this industry's use and disposition of approximately 250 additional nonconventional pollutants.

Before introducing extensive new data collection efforts, EPA reviewed in 1986 available information and identified missing information that would need to be obtained for the review and revision of current effluent limitations guidelines and standards for this industry. 3.2.1 summarizes the data and information already available to EPA prior to 1986. Sections 3.2.2 through 3.2.13 describe EPA's new data collection efforts.

3.2.1 Summary of Data Collection Efforts

Data collection efforts conducted by EPA prior to 1986 provided substantial information regarding manufacturing processes, water use, wastewater characteristics, and treatment technologies in the pharmaceutical manufacturing industry. Documentation of these efforts was reviewed in 1986 to identify data and information that would be useful to the effort to develop revised effluent limitations guidelines and standards for the pharmaceutical manufacturing industry. This review identified the following major sources of information:

- 308 Portfolio Survey. The original 308 Portfolio Survey was an invaluable source of information for developing an industry profile and characterizing industry wastes. It provided the first detailed information on conventional pollutant parameters in the industry's wastewater and wastewater flow characteristics. It was also the first major data source on the use and/or generation of priority pollutants by this industry.

The 308 Portfolio Survey was conducted in two phases. In the fall of 1977, EPA distributed the original questionnaire to members of the Pharmaceutical Manufacturers' Association (PMA). (Now the Pharmaceutical Research and Manufacturers Association, PhRMA.) The Agency then distributed a second questionnaire to the remainder of the industry in the spring of 1979.

- <u>PEDCo Reports</u>. In the late 1970s, and concurrent with the data-gathering efforts of the 308 Portfolio Survey, PEDCo Environmental, Inc. (PEDCo), reviewed available literature to identify priority pollutants associated with the production of various pharmaceutical products.(2)(3)(4)

- <u>OAQPS Study</u>. EPA's Office of Air Quality Planning and Standards (OAQPS), with the assistance of the PMA, conducted a survey to determine the use and disposition of the 10 largest volume volatile organic pollutants that each member company purchased in 1975.(5)

  In 1985, OAQPS, with the assistance of the PMA, obtained updated purchase and disposition data for selected solvents from PMA member companies.(6) These data were added to the same type of industry data collected by OAQPS in 1975.

- <u>Screening and Verification Sampling Program</u>. Beginning in 1978, EPA initiated the Screening and Verification Sampling Program, under which wastewater samples were collected from plants with manufacturing operations representative of the industry. Process and end-of-pipe wastewater samples were collected and analyzed for priority, conventional, and nonconventional pollutants in a two-phase program. The first phase, called the screening phase, involved sampling and analyzing the effluent from 26 plants to determine the presence of conventional, priority, and nonconventional pollutants. This phase was followed by a verification phase, in which multiple samples were collected over several days at five facilities to verify the presence of the pollutants detected during the screening phase. Data from the Screening and Verification Sampling Program, augmented by data collected more recently, were used by EPA to characterize pharmaceutical industry wastewater.

- <u>RSKERL/ADA Study</u>. In 1979, the Robert S. Kerr Environmental Research Laboratory at Ada, Oklahoma (RSKERL/ADA) conducted an applied research study entitled "Industry Fate Study."(7) The purpose of this report was to determine the fate of specific priority pollutants within a biological treatment system. During the study, priority pollutants associated with the manufacture of pharmaceuticals were identified at two industrial facilities.

- Toxic Volatile Organics (TVO) Questionnaire. In 1982, EPA distributed a survey to 15 pharmaceutical manufacturing facilities requesting analytical information on TVO levels in their process wastewater. The survey was limited to volatile organic priority pollutants only.

- Steam Stripper Sampling. In May of 1983, EPA collected influent and effluent wastewater samples from a packed column steam stripper and a steam distillation flash tank at Plant 12003. The study was conducted over a five-day period, and provided EPA with analytical data documenting the performance of this technology treating pharmaceutical manufacturing industry wastewaters.

- Pilot-Plant Carbon Study. In 1984, U.S. EPA's Water Engineering Research Laboratory (WERL) conducted a pilot-plant carbon study to determine constituents contributing to high chemical oxygen demand (COD) in pharmaceutical manufacturing industry effluents, and to evaluate the ability of activated carbon adsorption technology to reduce COD levels.

- Domestic Sewage Study. In 1985, EPA sampled a pharmaceutical manufacturing facility as part of its efforts to evaluate the discharge of priority and hazardous pollutants to POTWs.(1) Samples of the raw wastewater discharge to the local POTW were taken at Plant 30767 during a 24-hour period.

Data from the above sources were evaluated and summarized in 1986. Additional data collection efforts were then undertaken to fill the data gaps identified during the analysis of the above data and to update or replace outdated information. These data collection efforts were:

- A follow-up (to the 1984 WERL study) pilot plant carbon study in 1987;

- Sampling and analysis of wastewater at 13 pharmaceutical manufacturing facilities between 1986 and 1991;

- A screener questionnaire distributed in May 1989 and a detailed questionnaire distributed in September 1991;

- Industry self-monitoring data submitted to EPA with the Detailed Questionnaire;

- EPA bench- and pilot-scale steam stripping, air stripping, and distillation treatability studies in 1991 and 1993;

- Product patent reviews for solvent usage;

- POTW Survey distributed in 1993 to nine POTWs receiving wastewater from pharmaceutical manufacturers; and

- Annual pollutant disposition data submitted by industry for the years 1987 through 1990 as part of their requirements under 313 of the Emergency Planning and Community Right to Know Act of 1986 [Toxic Release Inventory (TRI) data].

These data were presented in the record supporting the rulemaking proposed on May 2, 1995. In response to the proposal, EPA received additional data from industry which was described in a Notice Of Availability (NOA) published on August 8, 1997. EPA received additional data from industry in comments on the NOA. Additional data collected by EPA since the May 2, 1995 proposal are summarized below:

- Advanced biological treatment data submitted by industry to EPA in response to the May 2, 1995 proposal;

- Steam stripping performance data submitted by industry to EPA in response to the May 2, 1995 proposal;

- Technology performance data for cyanide submitted by industry to EPA in response to the May 2, 1995 proposal;

- Site visits conducted in 1996 at five pharmaceutical manufacturing facilities and three POTWs;

- Sampling and analysis of wastewater at the Barceloneta Regional Wastewater Treatment Plant (BRWTP) in August 1996 and subsequent visits in April and August 1997;

- Ammonia nitrification data submitted to EPA by industry in response to the August 8, 1997 NOA; and

- Additional BPT data submitted to EPA by industry in response to the August 8, 1997 NOA.

Discussions of these additional data are presented in Sections 3.2.2 through 3.2.13.

3.2.2 Follow-Up Pilot-Plant Carbon Study

EPA conducted a follow-up pilot-plant powdered activated carbon (PAC) study in 1987. The purpose of the study was to reduce COD concentrations by using PAC in pharmaceutical manufacturing wastewater biological treatment systems without creating additional mixed liquor suspended solids in the wastewater.

3.2.3 EPA's 1986 - 1991 Sampling at Selected Pharmaceutical Manufacturers

Between 1986 and 1991, EPA conducted sampling episodes at 13 pharmaceutical manufacturing facilities to: 1) characterize the pollutants in the wastewater being discharged at direct and indirect discharging facilities, 2) collect pollutant treatment system performance data from facilities with well-operated biological treatment systems (those systems attaining better than BPT annual average effluent levels), and 3) obtain treatability data from steam stripping and distillation.

Prior to 1986, the Agency had focused on 5 conventional pollutants and 126 priority pollutants identified in the 1977 Consent Decree. In 1986, the Agency expanded the analysis of pharmaceutical manufacturing wastewater and wastewater treatment sludges to determine the presence and levels of all the pollutants on the "Industrial Technology Division (ITD) List of Analytes" (hereinafter, the "List of Analytes").

The List of Analytes was derived from the "ITD/RCRA List of Lists" (8) using the following criteria:

- All analytes on the List of Lists were included on the List of Analytes, except:
  - -- Analytes which only appear on the "Acutely Toxic Chemicals" List in EPA's Chemical Emergency Preparedness Program (VTOX list);
  - -- Analytes which hydrolyze or are destroyed by water;

- -- Analytes which are designated for analysis solely by high performance liquid chromatography (HPLC);
- -- Analytes which must be analyzed by a subset of their chemical structure, or derivatized (except for the phenoxy acid herbicides which are analyzed by Method 615); and
- -- Analytes for which no analytical standard is available.

- For analytes which hydrolyze, the hydrolysis product is included (if an analysis type and standard are available).
- Metal salts are included as the metal (e.g., beryllium, iron, sodium) and as the anion (e.g., F-, S-, CN-).

When the List of Analytes was first assembled in 1986, it contained 377 analytes.(9) The List of Analytes was expanded as the need to identify different analytes in the wastewater of different industries increased. The most recent List of Analytes was published again in 1990 and included 458 analytes.(10)

The List of Analytes was modified in the 1986-1991 sampling programs conducted for the pharmaceutical manufacturing industry to account for two program-specific needs:

1. After the first two sampling episodes (Nos. 1108 and 1111), EPA determined that it was not necessary to continue analyzing pharmaceutical manufacturing wastewater and wastewater treatment plant sludges for pesticides/herbicides (Method 1618) and dioxins/furans (Method 1613) unless the presence of these analytes was known or suspected. Pesticides/herbicides and dioxins/furans were not detected during the first two sampling episodes.

2. Analysis of volatile organic pollutants not on the List of Analytes was conducted on a site-specific basis after an assessment of the pre-sampling site visit information (i.e., information on solvent use by the pharmaceutical manufacturing facility). Pharmaceutical manufacturing industry wastewaters were characterized for additional analytes such as: ethanol, ethyl acetate, formaldehyde, isopropanol, isopropyl acetate, methanol, methyl formate, and petroleum naphtha.

During the sampling program, EPA gathered analytical data to characterize the wastewater from five direct dischargers and eight indirect dischargers. Treatment system performance data were gathered from three advanced biological treatment systems and two biological pretreatment systems. Treatment unit performance data documenting the performance of five steam stripping columns were gathered. The performance of one resin adsorption column and one cyanide destruction unit was also documented. Table 3-1 summarizes the types of facilities sampled and types of information collected.

Prior to each sampling episode, a presampling site visit was conducted to gather information on manufacturing operations, solvent usage, wastewater treatment systems, and possible sample point locations. Following each visit, a site visit report was prepared which documented the information gathered and provided recommendations regarding sample point locations. These site visit reports are included in the Record of this rulemaking.

A draft sampling plan was prepared before each sampling episode to document the procedures to be followed by the sampling crew during that episode. Prior to the sampling event, EPA sent the sampling plan to plant personnel for their review and comment. During the sampling episodes, sampling teams collected, preserved, and shipped the samples to an EPA-contracted laboratory according to established protocols defined in the sampling plan. EPA offered to split samples with facility personnel during all episodes.

Following each sampling episode, a sampling episode report was prepared to document facility manufacturing operations, sampling procedures followed, and analytical results obtained (including a QA/QC evaluation of these results), and also to provide a discussion of wastewater treatment plant operation and performance. Sampling plans and reports are also included in the Record of this rulemaking.

QA/QC evaluations of analytical data began at EPA's Sample Control Center (SCC) when the data were received from the contract laboratories. The raw data from the laboratories were reviewed for acceptability based on predefined data quality objectives specified in the respective analytical methods. The following objectives were reviewed:

- Sample completeness;
- Holding times;
- Calibration verification;
- Blanks;
- Matrix spikes;
- Matrix spike duplicates;
- Laboratory control samples; and
- ICP serial dilution.

After the above-mentioned criteria were reviewed by SCC, a data quality report was issued for each dataset. Datapoints deemed unacceptable by SCC were deleted from the dataset. Once the analytical data review was completed, a review was conducted to determine the following:

- The relative percent differences between split sample results;
- The ability to reproduce blind field duplicates; and
- Any significant deviations or upsets in process operations during the sampling event that may have impacted the results obtained.

Data not meeting QA/QC objectives with respect to blind field duplicates established by EPA for the analytical methods used were discussed in the respective sampling episode reports, and the impacted data were identified and deleted from the final database as appropriate.

3.2.4 Pharmaceutical Industry Questionnaires

The Pharmaceutical Manufacturing Industry Questionnaire distributed by EPA under authority of 308 of the Clean Water Act is a major source of data and information used in the development of effluent limitations guidelines and standards for the pharmaceutical manufacturing industry. This questionnaire requested information on:

- Pharmaceutical products and production processes;
- Chemical use and disposition;
- Wastewater treatment system design and operation parameters;

- Waste minimization/pollution prevention techniques;
- Wastewater characterization, including long-term self-monitoring data; and
- Financial and economic data for use in assessing economic impact and achievability of regulatory options.

EPA used a two-phase questionnaire approach to collect industry information including a screener questionnaire and a detailed questionnaire. The industry trade association PMA (now known as PhRMA) participated in the development of these questionnaires and both questionnaires were submitted to OMB for clearance. The screener questionnaire was distributed by EPA in May 1989 to 1,163 known or suspected pharmaceutical manufacturers. The screener questionnaire mailing list was developed after an extensive review of these sources:

- EPA current list of pharmaceutical manufacturers (respondents of the 308 Portfolio Survey in 1977 and 1979);
- List of pharmaceutical manufacturers maintained by Noyes Data Corporation (11);
- List of pharmaceutical manufacturers presented in the <u>Physician's Desk Reference</u> (12);
- List of pharmaceutical manufacturers presented in the <u>Merck Index</u> (13);
- List of facilities classified under SIC codes 2831, 2833, and 2834 in Dunn and Bradstreet's "Electronic Yellow Pages" (14);
- List of facilities classified under SIC codes 2831, 2833, and 2834 in Dunn and Bradstreet's <u>World Marketing Directory</u> (15);
- List of facilities classified under SIC codes 2831, 2833, and 2834 in the EPA Permit Compliance System (PCS);
- List of facilities classified: 1) as pharmaceutical manufacturers, or 2) under SIC codes 2831, 2833, and 2834 by state and/or regional wastewater permitting authorities; and
- List of pharmaceutical manufacturers published in the American Medical Association's <u>Drug Evaluations</u>.(16)

The screener questionnaire was designed to identify those facilities that could possibly be subject to the revised BPT, BAT, BCT, and PSES effluent limitations guidelines and standards. Detailed Questionnaires were then sent to pharmaceutical manufacturing facilities that were identified as: 1) direct dischargers of process wastewater involved in fermentation, natural extraction, chemical synthesis, or mixing, compounding, or formulating operations, or 2) indirect dischargers of process wastewater that potentially use solvents in the manufacturing process. Indirect dischargers that indicated in the screener that they use fermentation, extraction, or chemical synthesis process operations were assumed to potentially use solvents and were sent detailed questionnaires. In addition, the Detailed Questionnaire was sent to indirect dischargers utilizing mixing/compounding/formulating operations if the facility indicated in the screener that they used solvents in these operations. The Detailed Questionnaire was not sent to facilities reporting zero discharge or research only operations in the screener questionnaire.

EPA wanted to ensure that the questionnaire was designed to collect representative data from the industry in the form that the industry maintains the data. Therefore, specific pharmaceutical manufacturers, as well as their trade association (PMA), were involved in the development of the Detailed Questionnaire. The PMA was given copies of the original draft of the survey, as well as subsequent drafts that included significant revisions or modifications.

In 1989, nine plants (six PMA members and three non-PMA members) were sent the Detailed Questionnaire as part of the pretest program. However, one facility closed prior to receiving the questionnaire, and a second declined to participate in the pretest program. Industry comments from the remaining seven facilities were incorporated into the survey, and a revised version was prepared.

As required by the Paperwork Reduction Act, (44 U.S.C. 3501 et seq.), EPA submitted the Detailed Questionnaire to the Office of Management and Budget (OMB) for review, and published a notice in the Federal Register that the questionnaire was available for review and comment.(17) In August 1990, OMB granted clearance of the technical (Part A) and company-level financial information (Part B) of the Detailed Questionnaire. OMB denied clearance of questions asking for facility-specific economic information. Industry representatives argued that the industry should not be required to submit such information because it was not readily available because of standard accounting practices used by the industry, was highly sensitive, and in any case was not useful in developing effluent limitations guidelines. The Agency considered facility-level financial data critical to the economic analysis, and following discussions, OMB approved Part B of the questionnaire. Respondents to Part B had the option of certifying certain conditions about the economic impacts that will result from costs incurred to comply with the effluent limitations guidelines and standards that EPA ultimately promulgates pursuant to this rulemaking. This facility impact certification, signed by an official of the owner company with sufficient decision-making authority for this certification to be legally binding, could be submitted to EPA in lieu of completing the facility-level financial data in the Detailed Questionnaire.

In September 1991, EPA sent the Detailed Questionnaire to 280 facilities. This group included all direct dischargers involved in fermentation, extraction, chemical synthesis, or mixing, compounding, or formulating operations, all indirect dischargers involved in fermentation, extraction, and chemical synthesis operations, and a statistical sampling of indirect discharging facilities conducting mixing, compounding, or formulating operations that used solvents in their pharmaceutical manufacturing operations.

Not all indirect dischargers that performed mixing, compounding, or formulating operations were sent a Detailed Questionnaire. EPA determined this was unnecessary because the production methods, wastewater volume and strength, and treatment operations used among this group of facilities were similar. EPA expected the variation in the questionnaire responses from this group of facilities to be very small based on the information from the screener questionnaire supplied by this group of facilities. Consequently, a randomly selected subset of mixing, compounding, or formulating facilities that used solvents was surveyed. The random sample was developed using a methodology that ensured that the Detailed Questionnaire was distributed to facilities within four plant size groups, based on number of employees.(18)

Of the 280 facilities sent the Detailed Questionnaire, 245 were not closed or exempted and were deemed eligible to respond. Of the remaining 35 plants, 12 were closed and 23 were exempted from completing the questionnaire by EPA because they certified that they no longer manufactured pharmaceutical products and they had no plans to manufacture them in the future. EPA received responses from 244 of the 245 eligible facilities (a 99.6% response rate).

The Detailed Questionnaire was designed to gather data and information to develop revised BAT, BPT, and BCT effluent limitations guidelines and pretreatment standards (PSES, PSNS) intended to control priority and nonconventional volatile organic pollutants and any other conventional, priority and nonconventional pollutants of concern found in significant quantities (i.e., treatable concentrations). The Detailed Questionnaire gathered information on pharmaceutical production, chemical use and disposition, waste minimization and pollution prevention, wastewater generation, collection, and conservation, wastewater treatment, steam stripping, wastewater characteristics and economic and financial data.(19)

The Agency required product-specific information to better understand the industry discharge pattern for individual pollutants.

The on chemical use and disposition focused on a specific list of chemicals and compounds identified as associated with the pharmaceutical manufacturing industry. The specific list of 139 pollutants was created after review of the data and information sources then available to determine all priority and nonconventional pollutants that were known or suspected to be used in the manufacture of pharmaceuticals. The list of 139 included pollutants meeting at least one of the following criteria:

- Identified by the 1975 and/or 1985 the Office of Air Quality Planning and Standards (OAQPS) solvent use and disposition data as being discharged in pharmaceutical manufacturing industry wastewaters;
- Identified by the pharmaceutical product patent search as potentially being used in pharmaceutical manufacture;
- Detected in the wastewaters of the pharmaceutical manufacturing industry;
- Identified as a volatile organic pollutant contained on the DSS list of analytes;

- Identified as a volatile organic pollutant on the ITD List of Analytes; or
- Identified as a volatile organic pollutant that was present in pharmaceutical manufacturing industry wastewaters according to the TRI database.

The Agency used the information on chemical use and disposition to provide wastewater loading estimates for various pollutants and to evaluate individual chemical usage by pharmaceutical manufacturers. In addition, OAQPS evaluated the chemical emission information in support of its development of emission standards for hazardous air pollutants as required by the Clean Air Act. The Agency's Office of Pollution and Prevention (OPP) also evaluated the responses to determine the extent to which individual chemicals are recycled and reused. Pollution prevention information on the extent to which source reduction and recycling is practiced in the pharmaceutical industry has been incorporated into EPA's regulatory development efforts to identify pollution prevention practices which have the potential for success.

Responses to questions pertaining to wastewater generation and collection have been used by EPA to characterize wastewater generation by the industry and to develop appropriate plant-by-plant treatment costs for process wastewater. EPA has used the information on wastewater treatment present at pharmaceutical facilities to determine the basis for revised regulations and to develop regulatory option costs. The information about the design and operating characteristics of in-place technology was also used for establishing the technology basis of the regulatory options considered and for cost estimating purposes. In addition, the existing wastewater treatment information was used to estimate air emissions from the treatment of pharmaceutical manufacturing wastewaters.

The Agency realizes that steam stripping technology is being used by some pharmaceutical manufacturing facilities primarily to recover volatile organic compounds from wastewater. Consequently, the Agency solicited data on steam strippers to categorize as accurately as possible those units in place at pharmaceutical manufacturing plants to identify their design and operating parameters. The information provided on steam stripping has been used by EPA to evaluate what constitutes BAT level steam stripping under the Clean Water Act, as well as MACT level steam stripping under the Clean Air Act.

Conventional wastewater characteristics, including long-term performance averages supported by individual data points, were used by the Agency to develop revised limitations and standards for conventional pollutants. The Agency requested organics data to confirm the presence of priority and nonconventional pollutants that were expected in discharges of pharmaceutical manufacturing processes and to provide a source of treatment performance data for EPA's regulatory development.

The Agency used economic and financial data collected with the questionnaire to evaluate the economic impact of proposed regulations on the industry and to determine whether PSNS/NSPS would create a barrier to entry for facilities wishing to enter into pharmaceutical manufacturing.

3.2.5 Industry-Supplied Data

Facilities that discharge wastewater directly to surface waters of the United States must have a National Pollutant Discharge Elimination System (NPDES) permit, which establishes effluent limitations for various pollutants and requires the plants to monitor the levels of such pollutants in their effluent (see 402 CWA, as amended, implemented by 40 CFR 121-125). POTWs also require facilities to monitor pollutant levels in their wastewater prior to discharge. Additionally, some facilities with treatment systems monitor intermediate points within the systems to check the efficiency of the unit. EPA requested that copies of the effluent monitoring data collected by plants in 1990 be submitted as part of the response to the Detailed Questionnaire. Data from treatment systems using the technologies described in 7 were entered into a database to establish the treatment performance of those technologies.

Some facilities and POTWs provided additional data in response to a specific request by EPA or as follow-up to the data provided in their questionnaire or data gathered during a sampling episode. These additional data submittals are explained in the following paragraphs.

In addition to the data submitted by Plant 30701 in their Detailed Questionnaire response, an additional 20 months of self-monitoring data were submitted to EPA from that direct discharger. The data were submitted by plant personnel because they felt that the pharmaceutical production reported in their response to the 1988 pre-test questionnaire was below normal levels. EPA statisticians analyzed the original questionnaire data and the additional 20 months of data. Since no significant differences between the datasets were found, the two datasets were combined, and used in the wastewater characterization of the industry.

In 1991, under authority of 308 of the Clean Water Act, EPA requested that Facility 30542 provide six months' worth of data documenting the performance of their cyanide destruction unit. Personnel from Plant 30542 collected and analyzed influent and effluent samples from their batch cyanide destruction (hydrogen peroxide oxidation) unit for six months. These data were submitted to EPA in November of 1991, and were used in the evaluation of effluent limitations guidelines and standards for cyanide based on cyanide destruction technology.

In March of 1989, EPA conducted concurrent sampling episodes at Facility 30977 and the POTW to which they discharged. After those sampling episodes, POTW personnel provided EPA with additional priority and nonconventional pollutant data as well as data collected characterizing the wastewater discharged from Facility 30977. These data were ultimately used for wastewater characterization of the pharmaceutical manufacturing industry.

When personnel from Facility 30832 indicated that the data collected by EPA during a sampling episode in July of 1986 were not representative of their typical effluent, EPA requested from the POTW to which that facility discharged, copies of long-term data collected over a 12-month period. The data submitted by the POTW were added to EPA's database, and have been used to help characterize pharmaceutical manufacturing wastewaters. Based on comparison to the long-term data, the data collected during the sampling episode were judged not to be representative of typical operations at Facility 30832, and were not used in the development of effluent limitation guidelines and standards.

3.2.6 Air Stripping, Steam Stripping, and Distillation Pilot Studies

Between October and December 1991, bench-scale and pilot-scale tests were conducted by EPA to study: 1) air stripping technology for ammonia removal from pharmaceutical manufacturing plant final effluent, and 2) steam stripping technology for volatile organic pollutant removal from pharmaceutical manufacturing plant process wastewaters.

The air stripping and steam stripping pilot studies were conducted at a pharmaceutical manufacturing facility with fermentation, chemical synthesis, formulation, and research operations. The total facility effluent was used as the feed to the pilot-scale air stripping study. The objective of this study was to examine the feasibility of obtaining at least 90% ammonia removal using air stripping technology. The wastewater characterization and treatment performance from the pilot-scale study are described in more detail in Sections 5 and 8, respectively.

For the steam stripping study, three wastewater streams from the facility were selected for analysis. The objective of this study was to achieve the lowest practical concentrations of volatile organic contaminants in the treated effluent, and to collect sufficient data to document these concentrations. On-site pilot-scale testing was conducted for two of the three streams. Bench-scale testing of the third wastewater was conducted at a contractor's laboratory because there was insufficient wastewater volume available at the facility to run the steam stripping test on a pilot-scale basis. The wastewater characterization and treatment performance from the steam stripping study are described in more detail in Sections 5 and 8, respectively.

In September 1993, EPA conducted an on-site treatment performance study using a pharmaceutical manufacturing facility's existing distillation column that treated wastewaters containing methanol. The objective of the study was to define operating parameters which resulted in optimum removal of methanol and compounds with similar volatility from wastewater and to collect sufficient data to document this removal. Waste characterization and treatment performance of the distillation study are discussed in Sections 5 and 8, respectively.

3.2.7 Patent Reviews

To better characterize volatile organic pollutant usage in the pharmaceutical manufacturing industry, EPA reviewed all patents identified for the approximately 1,300 pharmaceutical active ingredients identified as being manufactured. In 1987 the patents were reviewed for solvents on the ITD List of Compounds. The patents were reviewed again in 1991 to identify all solvents potentially used by the industry (not just those on the ITD List of Compounds). These patent reviews provided information regarding which volatile organic pollutants were most likely used in the manufacture of pharmaceutical products, and identified the plants at which the volatile organic pollutants were being used. EPA used patent search information to support the development of the List of Pollutants analyzed for sampling efforts and for questionnaire development.

3.2.8 POTW Survey

In 1993 EPA surveyed nine POTWs to investigate the effect that indirect discharging pharmaceutical manufacturing facilities had on the POTWs that received the wastewater. This survey contained questions about local limits or special conditions which apply to pharmaceutical manufacturing facilities and volatile or semivolatile organics which caused problems for POTWs. The POTWs were also asked to explain problems connected with discharges from pharmaceutical manufacturing operations which they felt needed to be addressed in national regulations, and to supply other information regarding pharmaceutical manufacturing facility discharges within the sewer district that bears on the need for pretreatment standards.

Substantive responses were received from six of the surveyed POTWs. The responding POTWs provided EPA with a list of the pollutants frequently found in their wastewater, details of problems that result when wastewaters containing slug loads of pollutants are discharged, comments on the structure of PSES, and monitoring requirements which would be helpful to POTWs. The detailed responses to the POTW survey are included in the Record for this rulemaking.

3.2.9 Toxic Release Inventory (TRI) Data

Facilities which manufacture or use in their process at least 25,000 pounds of a listed toxic chemical must submit the Toxic Chemical Release Inventory (TRI) Reporting Form as required by 313 of the Emergency Planning and Community Right-to-Know Act. This form, known as Form R, provides the public with information on the releases of listed toxic chemicals in their communities and provides EPA with information to determine the need for future regulations.(20) The quantities of both routine and accidental releases of listed toxic chemicals must be reported, as well as the maximum amount of the listed toxic chemical on site during the calendar year and the amount contained in wastes transferred off site. The Agency reviewed the information provided by the TRIs for the years 1987 through 1990 and for 1994 to assist in characterizing the chemical use and wastewater discharges from the industry, and to investigate current trends in chemical use and disposition in the pharmaceutical manufacturing industry.

3.2.10 Industry Data in Response to Proposed Rulemaking

In response to the proposed rulemaking published on May 2, 1995, EPA has acquired a significant amount of additional data and information from the industry. The new data submitted include: 1) Biochemical Oxygen Demand (BOD_5), Chemical Oxygen Demand (COD), and Total Suspended Solids (TSS) data for advanced biological treatment systems; 2) data on ammonia nitrification in advanced biological treatment systems; 3) advanced biological treatment systems data for organic pollutants; 4) steam stripping performance data for volatile organic pollutants; and 5) technology performance data for treatment of cyanide. Below are summaries of each type of new data provided by industry.

Advanced Biological Treatment Data (Biochemical Oxygen Demand (BOD_5), Chemical Oxygen Demand (COD), Total Suspended Solids (TSS) and Ammonia)

Additional BOD_5, COD, and TSS data were submitted with comments on the proposed effluent limitations guidelines and standards from five facilities. The data from three of the facilities represents additional years of data that supplement the 1990 year data that were previously part of the technology performance database for advanced biological treatment. Data from one other facility represents a new source of BOD_5, COD, TSS performance data which was also added to the advanced biological treatment technology performance database. Data from the fifth facility included only one data pair that was not included in technology performance database. A discussion of the review of these new data and the evaluation of whether to include them in the technology performance database is presented in 8.3.

Nitrification in Advanced Biological Treatment Data for Ammonia.

Performance data on ammonia nitrification from one facility were used as the basis of ammonia limitations at proposal. This facility provided additional ammonia data for a multi-year period. Three other facilities also submitted ammonia nitrification data in response to the proposed rulemaking. The other new ammonia data from biological treatment have been added to the existing ammonia database.

Advanced Biological Treatment Organics Data

New biological treatment performance data for organic pollutants were submitted with comments on the May 2, 1995 proposal by six facilities. Four of these facilities represented performance of advanced biological treatment.

Steam Stripping Performance Data

New data representing the performance of steam stripping technology in removing volatile organic pollutants were submitted with comments on the May 2, 1995 proposal by three facilities. The additional data reflect treatment by four stream strippers of 23 of the pollutants for which standards were proposed. In response to the comments on the May 2, 1995 proposal related to steam stripping of volatile organics, EPA has incorporated the newly submitted data with the data used at proposal and revised its pretreatment standards for the various parameters.

Technology Performance Data for Cyanide

EPA received additional cyanide treatment performance data from three facilities. Two of these facilities use alkaline chlorination treatment and one of these facilities uses hydrolysis treatment. For one facility, the new data include the individual effluent data points corresponding to the facility's 308 Questionnaire average 1990 effluent cyanide concentration. For the second facility, the new data include: 1) part of the raw 1990 data used in developing the facility's 308 Questionnaire average effluent cyanide concentration (the other part of the raw 1990 data used in the reported averages could not be located by the plant) and 2) additional 1994 cyanide destruction data. For the third facility, the new data include 1994 cyanide destruction data. In response to the May 2, 1995 proposal comments related to cyanide, EPA has incorporated the newly submitted data with the data used at proposal in its evaluation of cyanide.

3.2.11 Site Visits

Since the May 2, 1995, proposal, EPA has performed site visits at five facilities and three POTW's. The site visits were performed at four pharmaceutical manufacturers which discharge to a POTW and one pharmaceutical manufacturer which discharges directly to a surface water body. The respective POTW's were visited to collect information on the issues that affect indirect dischargers. A summary of the sites visited and the types of information collected are shown below:

Site	Date of Visit	Information Collected			
		WW Treatment	Mfg. Operations	Research/Pilot-Plant Operations	Indirects-Regulatory Issues
Abbott Laboratories	4/12/96 - 4/14/96	X	X	X	X
North Shore Sanitary District	4/12/96 - 4/14/96	X			X
Pfizer, Inc.	8/20/96 - 8/21/96	X	X	X	
Ganes Chemicals	11/19/96 + 11/22/96	X	X		X
Bergen County Utilities Authority	11/19/96 + 11/22/96	X			X
ISP Van Dyk	11/20/96 - 11/21/96	X	X		X
Penick Corp.	11/20/96 - 11/21/96	X	X		X
Passaic Valley Sewerage Commissioners	11/20/96 - 11/21/96	X			X

3.2.12 Barceloneta Regional Wastewater Treatment Plant (BRWTP) Sampling Effort

On May 24, 1996, an engineering site visit was conducted at the Barceloneta Regional Wastewater Treatment Plant (BRWTP) located in Barceloneta, Puerto Rico in preparation for sampling at this plant. A sampling episode was performed at the BRWTP from August 10 through August 16, 1996. The purpose of the sampling trip was to characterize the mass balance of specific organics around the primary treatment units and to characterize the treatment of COD and ammonia across the entire treatment plant.

A portion of the sampling episode, conducted jointly with representatives of PhRMA, also focused on determining the aerobic and anoxic biodegradation rates for the seven pollutants of concern in the primary treatment units. The quantity of mass reduction attributed to biodegration can be determined from the aerobic and anoxic biodegradation rates. The aerobic and anoxic rates were determined through lab studies conducted on samples taken during the sampling episode. The biodegradation rates were determined for each of the seven pollutants of concern across the grit chamber and the primary clarifier. A sampling episode by PhRMA was conducted in April 1997 to supplement the August 1996 anoxic biodegradation data. An additional sampling episode by PhRMA was conducted in August 1997 to enhance the mass balance data for alcohol losses through the primary clarifier.

3.2.13 Industry Data in Response to Notice of Availability

Lastly, since the August 8, 1997 Notice of Availability (NOA), EPA has received additional data from six facilities regarding nitrification/denitrification. Additional data were submitted with comments on the NOA. These data included a pilot-plant study on nitrification, data on two-stage nitrification from two facilities, and data on single-stage nitrification from two facilities. EPA also received operating data from one facility on a nitrification feasibility study. Data from influent and effluent sampling points as well as design data and operating specifications were provided.

EPA has also received data from three facilities regarding conventional pollutant treatment. Additional data were submitted in addition to comments on the NOA. The data from these facilities are supplemental to data previously provided. Data from influent and effluent sampling points were provided.

3.3 Overview of the Industry

This provides an overview of the pharmaceutical manufacturing industry by presenting general information on the geographical locations of facilities, Standard Industrial Classification (SIC) code distribution, value of shipments and number of employees in the industry, and age of facilities.

3.3.1 Geographical Location of Manufacturing Facilities

According to the 1989 Pharmaceutical Screener Questionnaire and the 1990 Detailed Questionnaire, there are 304 pharmaceutical facilities with solvent use which discharge wastewater in 34 states and the Commonwealth of Puerto Rico. This number includes the 244 facilities which completed the Detailed Questionnaire and the 60 indirect dischargers with mixing, compounding, or formulating operations which were not sent the Detailed Questionnaire. The majority of pharmaceutical manufacturing facilities are located in the eastern half of the United States, with the highest concentration of facilities in New Jersey, New York, Pennsylvania, and Puerto Rico. A map of the United States with the number of pharmaceutical manufacturing facilities in each state (or commonwealth) is presented in Figure 3-1. Table 3-2 presents the number of pharmaceutical manufacturing facilities by state and EPA region, along with the percentage of total facilities in each state and EPA region, and the total number of employees in each EPA region.

3.3.2 SIC Code Distribution

Standard Industrial Classification (SIC) codes, established by the U.S. Department of Commerce, are classifications of commercial and industrial establishments by the type of activity in which

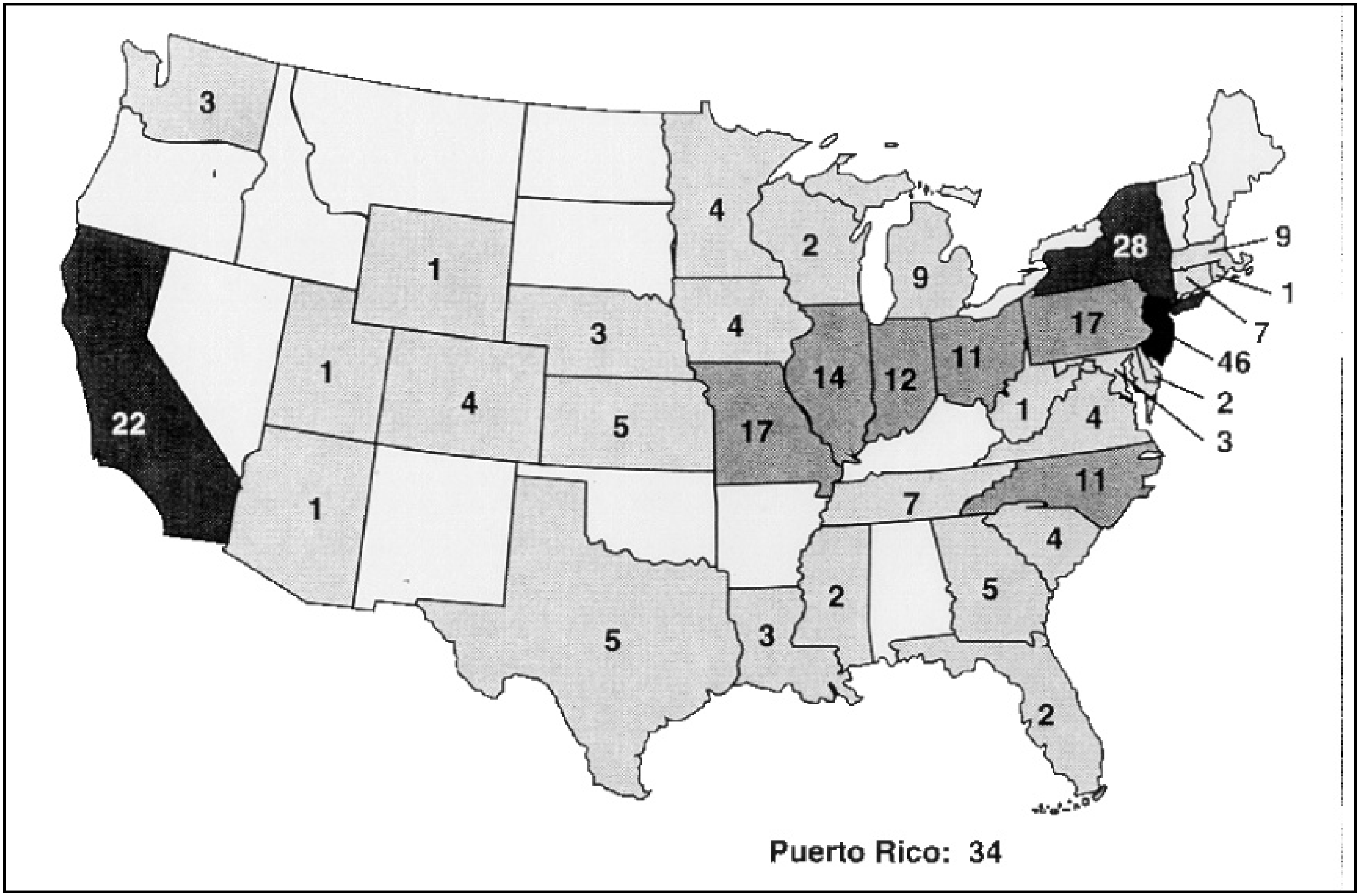

Figure 3-1. Location of Operating Pharmaceutical Facilities by State (304 Facilities)

they engage. The primary purpose of SIC codes is to classify the manufacturing industries for the collection of economic data. An operating establishment is assigned an industry code on the basis of its primary activity, which is determined by its principal product or group of products. The principal product of a manufacturing establishment is determined by the value of production. Pharmaceutical manufacturing facilities generally cover SIC codes 2833, 2834, and/or 2836 (formerly 2831). Other products included under the definition of pharmaceutical manufacturing facilities are discussed in 3.4.

3.3.3 Value of Shipments and Number of Employees in the Industry

The Department of Commerce provided information on the value of shipments and the number of total employees in the pharmaceutical manufacturing industry by SIC code.(21) In 1991, the value of product shipments for SIC codes 2833, 2834, and 2836 were $6.25 billion, $37.4 billion, and $2.84 billion, respectively. In 1991, the total number of employees in the pharmaceutical industry for SIC codes 2833, 2834, and 2836 were 12,500, 129,100, and 12,100, respectively.

3.3.4 Age of Facilities

Table 3-3 presents a distribution of pharmaceutical manufacturing facilities by decade when operations began at the facility and when pharmaceutical manufacturing operations began at the facility. The majority of facilities which currently manufacture pharmaceuticals began such operations after 1960. The oldest reported pharmaceutical manufacturing operation began in 1879, while the most recent operation reported began in 1991.

3.4 Pharmaceutical Manufacturing Processes

The pharmaceutical manufacturing industry encompasses the manufacture, extraction, processing, purification, and packaging of chemical materials to be used as medication for humans and animals. For this rulemaking, EPA has defined the pharmaceutical manufacturing industry to include the manufacture of any of the following products:

- Biological products covered by the U.S. Department of Commerce, Bureau of the Census Standard Industrial Classification (SIC) Code No. 2836, with the exception of diagnostic substances. (Products covered by SIC Code No. 2836 were formerly covered under the 1977 SIC Code No. 2831.)

- Medicinal chemicals and botanical products covered by SIC Code No. 2833.

- Pharmaceutical products covered by SIC Code No. 2834.

- All fermentation, biological and natural extraction, chemical synthesis and formulation products considered to be pharmaceutically active ingredients by the Food and Drug Administration that are not covered by SIC Code Nos. 2833, 2834, or 2836.

- Multiple end-use products derived from pharmaceutical manufacturing operations (e.g., components of formulations, intermediates, or final products, provided that the primary use of the product is intended for pharmaceutical purposes).

- Products not covered by SIC Code Nos. 2833, 2834, and 2836 or other categorical limitations and standards if they are manufactured by a pharmaceutical manufacturer by processes that generate wastewaters that in turn closely correspond to those of pharmaceutical products. (An example of such a product is citric acid.)

- Cosmetic preparations covered by SIC Code No. 2844 that contain pharmaceutically active ingredients or ingredients intended for treatment of some skin condition. (This group of preparations does not include products such as lipsticks or perfumes that serve to enhance appearance or to provide a pleasing odor, but do not provide skin care. In general, this also excludes deodorants, manicure preparations, shaving preparations and non-medicated shampoos that do not function primarily as a skin treatment.)

Products or activities specifically excluded from the pharmaceutical manufacturing category are:

- Surgical and medical instruments and apparatus reported under SIC Code No. 3841.

- Orthopedic, prosthetic, and surgical appliances and supplies reported under SIC Code No. 3842.

- Dental equipment and supplies reported under SIC Code No. 3843.

- Medical laboratories services reported under SIC Code No. 8071.

- Dental laboratories services reported under SIC Code No. 8072.

- Outpatient care facility services reported under SIC Code No. 8081.

- Health and allied services reported under SIC Code No. 8091, and not classified elsewhere.

- Diagnostic devices other than those reported under SIC Code No. 3841.

- Animal feeds that include pharmaceutical active ingredients such as vitamins and antibiotics, where the major portion of the product is non-pharmaceutical, and the resulting process wastewater is not characteristic of process wastewater from the manufacture of pharmaceutical products.

- Foods and beverage products fortified with vitamins or other pharmaceutical active ingredients, where the major portion of the product is non-pharmaceutical, and the resulting process wastewater is not characteristic of process wastewater from the manufacture of pharmaceutical products.

- Pharmaceutical products and intermediates subject to the provisions of 40 CFR part 414, provided their manufacture results in less than 50 percent of the total flow of process wastewater that is regulated by 40 CFR part 414 at the facility.

3.4.1 Types of Pharmaceutical Processes and Products

There are four general types of manufacturing processes used by pharmaceutical manufacturing facilities. The four process types are: fermentation, biological and natural extraction, chemical synthesis, and mixing, compounding, or formulating. Figure 3-2 presents a bar graph of the number of facilities which use each type of manufacturing process. Table 3-4 presents examples of typical products from each type of manufacturing process.

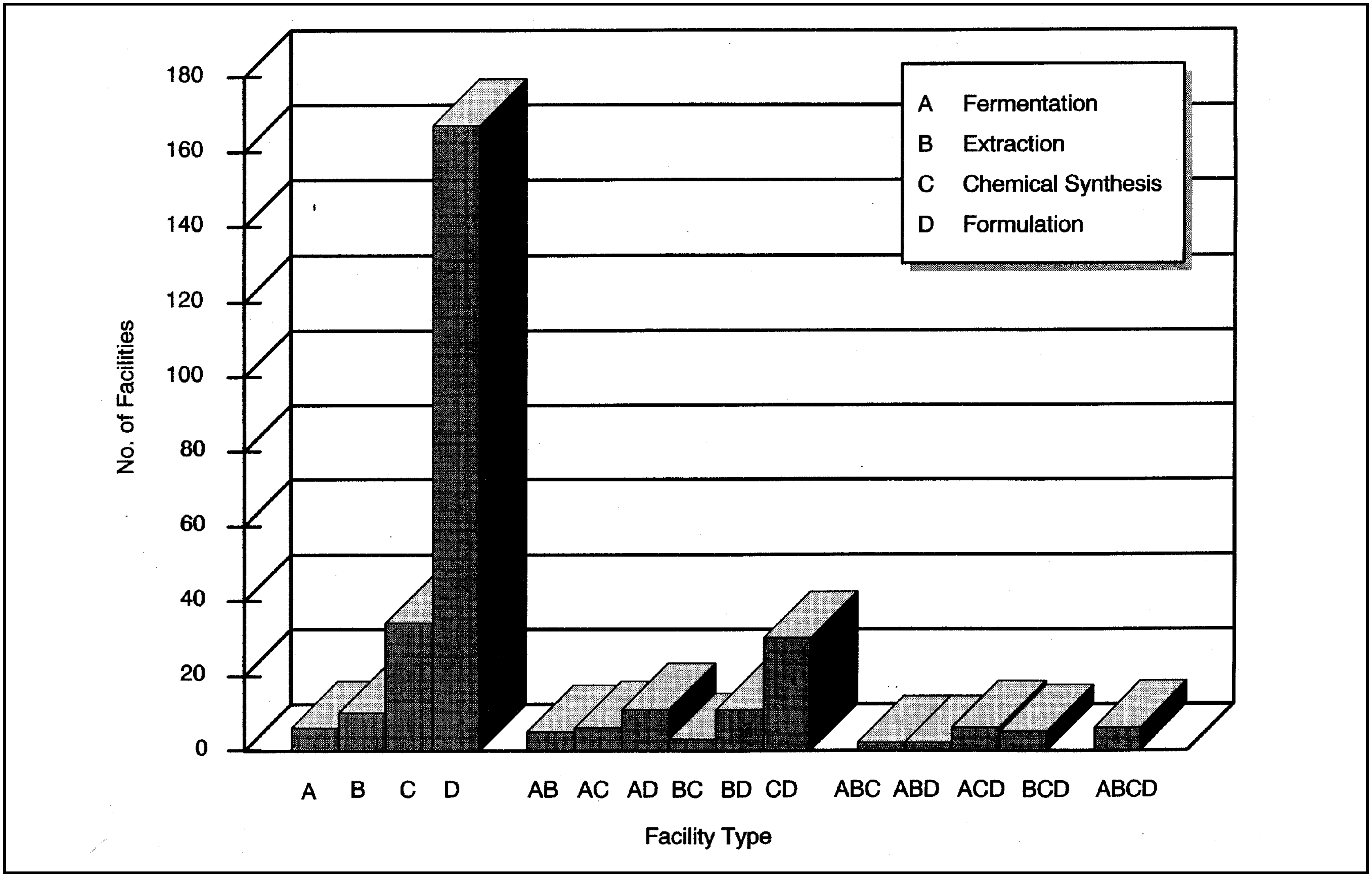

Figure 3-2. Number of Facilities in Each Combination of Pharmaceutical Manufacturing Process Types

3.4.2 General Process Descriptions

General process descriptions for each type of process operation are described in the following subsections. The specific processing steps on individual process lines may differ from these general descriptions as process operations will be tailored to the specific product being produced.

3.4.2.1 Fermentation

Most antibiotics and steroids are produced by the fermentation process, which involves three basic steps: inoculum and seed preparation, fermentation, and product recovery. Production of a fermentation pharmaceutical begins in the seed preparation step with spores from the plant master stock. The spores are activated with water, nutrients, and warmth; they are then propagated through the use of agar plates, test tubes, and flasks until enough mass is produced for transfer to the seed tank. In some fermentations, a single seed tank may provide inoculum for several fermentations. In this type of operation, the seed tank is never emptied completely, so the remaining seed serves as the inoculum for the next batch. The seed tank is emptied, sterilized, and reinoculated only when contamination occurs.

Fermentation is conventionally a large-scale batch process. The fermentation step begins with a water wash and steam sterilization of the fermenter vessel. Sterilized nutrient raw materials in water are then charged to the fermenter. Microorganisms grown from seed to aid in the fermentation process are transferred to the fermenter from the seed tank and fermentation begins. During fermentation, air is sparged into the batch and temperature is carefully controlled. After a period that may last from 12 hours to one week, the fermenter batch whole broth is ready for filtration. Filtration removes mycelia (i.e., remains of the microorganisms), leaving the filtered aqueous broth containing product and residual nutrients that are ready to enter the product recovery phase.

There are three common methods of product recovery: solvent extraction, direct precipitation, and ion exchange or adsorption. Solvent extraction is a recovery process in which an organic solvent is used to remove the pharmaceutical product from the aqueous broth and form a more concentrated solution. With subsequent extractions, the product is separated from any contaminants. Further removal of the product from the solvent can be done by either precipitation, solvent evaporation, or further extraction processes. Normally, solvents used for product recovery are recovered and reused. However, small portions left in the aqueous phase during the solvent "cut" can appear in the plant's wastewater stream. Based on information from the Detailed Questionnaire, the solvents most often used in fermentation operations are acetone, methanol, isopropanol, ethanol, amyl alcohol, and MIBK. Table 3-5 lists solvents used in fermentation operations.

Direct precipitation using heavy metal precipitating agents is another common method of product recovery. The method involves first precipitating the product as a metal salt from the aqueous broth, then filtering the broth, and finally extracting the product from the solid residues. Copper and zinc are priority pollutant metals known to be used in the precipitation process.(2)

Ion exchange or adsorption involves removal of the product from the broth, using solid materials such as ion exchange resin, adsorptive resin, or activated carbon. The product is recovered from the solid phase using a solvent, then recovered from the solvent by evaporation.

Occasionally, a fermentation batch becomes infested with a phage, a virus that attacks microorganisms necessary to the fermentation process. Phage infection is rare in a well-operated plant, but when it occurs, the plant may discharge very large amounts of wastewater in a short period of time because of the decontamination process. Typically, the infested batch is discharged early, and its nutrient pollutant concentration is higher than that of spent broth.

Steam is the major sterilizing medium for most equipment. However, detergents and disinfectants, to the extent that they are used, can contribute to waste loads. An example of a commonly used chemical disinfectant is phenol, a priority pollutant. Air pollution control equipment sometimes installed to clean fermentation waste off-gas is another wastewater source. The air and gas vented from the fermenters usually contain odoriferous substances (e.g., oxides of nitrogen and sulfur) and large quantities of carbon dioxide. Treatment is often necessary to deodorize the gas before release to the atmosphere. Some plants use incineration methods; others use liquid scrubbers. The blowdown from scrubbers may contain absorbed chemicals, soluble organic compounds, and insoluble organic oils and waxes.

Spent fermentation broth contributes pollutants to wastewater from the food materials contained in the broth, such as sugars, starches, protein, nitrogen, phosphate, and other nutrients. Fermentation wastes are very amenable to biological treatment. The spent broth can be satisfactorily handled by biological treatment systems in a concentrated form. Equalizing the broth prior to treatment helps avoid system upsets that may occur if the biota receive too high feed concentrations at one time.

Data from the Detailed Questionnaire generally show that process wastewater from fermentation plants is characterized by high BOD_5, COD, and TSS concentrations; relatively large flows; and a pH range of approximately 4.0 to 8.0.

3.4.2.2 Biological and Natural Extraction

Many materials used as pharmaceuticals are derived from such natural sources as the roots and leaves of plants, animal glands, and parasitic fungi. These products have numerous and diverse pharmaceutical applications, ranging from tranquilizers and allergy-relief medications to insulin and morphine. Also included in this group is blood fractionation, which involves the production of plasma and its derivatives.

Despite their diversity, all extractive pharmaceuticals have a common characteristic: they are too complex to synthesize commercially. They are either very large molecules, and/or their synthesis results in the production of several stereoisomers, only one of which has pharmacological value. Extraction is an expensive manufacturing process which requires collecting and processing large volumes of specialized plant or animal matter to produce small quantities of products. Facilities utilize extraction when there are no other reasonable alternatives for producing a desired active ingredient.

The extraction process consists of a series of operating steps beginning with the processing of a large quantity of natural or biological material containing the desired active ingredient. After almost every step, the volume of material being handled is reduced significantly. In some processes, reductions may be in orders of magnitude, and complex final purification operations may be conducted on quantities of materials only a few thousandths of the volume handled in earlier steps. Neither continuous processing methods nor conventional batch methods are suitable for extraction processing. Therefore, a unique assembly-line, small-scale batch processing method is used. Material is transported in portable containers through the plant in 75- to 100-gallon batches. A continuous line of containers is sent past a series of operating stations. At each station, operators perform specific tasks on each batch in turn. As the volume of material being handled decreases, individual batches are continually combined to maintain reasonable operating volumes, and the line moves more slowly. When the volume is reduced to a very small quantity, the containers also become smaller, with laboratory-size equipment used in many cases. An extraction plant may produce one product for a few weeks; then, by changing the logistical movement of containers and redefining tasks to be conducted at each station, the plant can convert to the manufacture of a different product.

Residual wastes from an extraction plant essentially will be equal to the weight of raw material, since the active ingredients extracted are generally present in the raw materials at very low levels. Solid wastes are the greatest source of the pollutant load; however, solvents used in the processing steps can cause both air and water pollution. Detergents and disinfectants used in equipment cleaning operations are normally found in the wastewater.

Priority pollutants, including methylene chloride, toluene, chloroform, 1,2-dichloroethane, and phenol, were identified as being used in the manufacturing of extractive pharmaceuticals in the Detailed Questionnaire. The cations of lead and zinc are known to be used as precipitating agents. Phenol was identified as a disinfecting chemical. The other priority pollutants found were used as processing solvents. The Detailed Questionnaire identified nonconventional pollutants most often used in the extractive manufacturing process as ethanol, methanol, n-amyl acetate, isopropanol, and acetone. These nonconventional pollutants may be used as processing solvents. Table 3-6 lists solvents used in biological or natural extraction operations.

Solvents are used in two ways in extraction operations. Some solvents are used to remove fats and oils that would contaminate the products. These "defatting" extractions use an organic liquid that dissolves the fat but not the product material. Solvents are also used to extract the product itself. For example, when plant alkaloids are treated with a base, they become soluble in such selected organic solvents as benzene, chloroform, and 1,2-dichloroethane.

Ammonia is used in many extraction operations because it is necessary to control the pH of water solutions from both animal and plant sources to separate valuable components from waste materials. Ammonium salts are used as buffering chemicals, and aqueous or anhydrous ammonia is used as an alkalinizing reagent. The high degree of water solubility of ammonium salts prevents unwanted precipitation of salt, and they do not react chemically with animal or plant tissue. Such basic materials as hydroxides and carbonates of alkali metals do not have these advantages.

The principal sources of wastewater from biological/natural extraction operations are: 1) spent raw materials (e.g., waste plasma fractions, spent media broth, plant residues); 2) floor and equipment wash water; 3) chemical wastes (e.g., spent solvents); and 4) cleanup of spills.

Wastewater from extraction plants is generally characterized by low BOD_5, COD, and TSS concentrations; small flows; and pH values of approximately 6.0 to 8.0.

3.4.2.3 Chemical Synthesis

Most of the active ingredients marketed and sold as drugs are manufactured by chemical synthesis. Chemical synthesis is the process of manufacturing pharmaceuticals using organic and inorganic chemical reactions. Since most of these compounds are produced in batch operations, the conventional batch reaction vessel is the major piece of equipment used on the process line.

The reaction vessel is one of the most standardized equipment designs in the industry. Generally, it is made of either stainless steel or glass-lined carbon-steel, and it contains a carbon-steel outer shell suitable for either cooling water or steam. Inside the vessel is a motor-driven agitator and a baffle. Vessels of this type are made in many different sizes, with capacities ranging from 0.02 to 11.0 m^3 or more.

The basic vessels may be fitted with different attachments depending on the process needs of the product to be manufactured. Baffles usually contain sensors to measure the temperature of the reactor contents. Dip tubes may be used to introduce reagents into the vessels below the liquid surface. The vessel's agitators may be powered by two-speed motors or by variable-speed motor drives. The reactor may be mounted on load cells to accurately weigh the reactor contents. The batch reactors are typically installed with only the top heads extending above the plant operating floor to provide the operator with easy access for loading and cleaning. Also, one of the top nozzles may be fitted with a floodlight and another with a glass cover to enable an operator to observe the reactor contents.

The reactors can be modified for additional uses. By using heating or refrigeration devices, the chemicals may be boiled or chilled in them, according to process needs. By adding reflux condensation equipment, the vessel may perform complete reflux operations (i.e., recycling of condensed vapors). The vessels can also become evaporators if vacuum is applied. The reactors may also be used to perform solvent extraction operations and, by operating the agitator at a slow speed, the vessels can serve as crystallizers.

Synthetic pharmaceutical manufacture consists of using one or more of these reactor vessels to perform, in a step-by-step fashion, the various operations necessary to make the product. Following a definite recipe, the operator (or, increasingly, a programmed computer) adds reagents; increases or decreases the flow rate of cooling water, chilled water, or steam; and starts and stops pumps which transfer the reactor contents to another vessel. At appropriate steps in the process, solutions are pumped either through filters or centrifuges, or into solvent recovery headers or waste sewers.

The reactor vessels with an assembly of auxiliary equipment are usually arranged into independent process units, which are suitable for the complete or partial manufacture of many different pharmaceutical compounds. Only with the highest volume products is the process unit "dedicated" to manufacturing only one product. Large pharmaceutical plants may have many such units, while smaller plants may have only one or two.

Each pharmaceutical product is usually manufactured in a "campaign," in which one or more process units are used for a few weeks or months to manufacture enough compound to satisfy the projected sales demand. Campaigns are usually tightly scheduled, with detailed coordination extending from procurement of raw materials to packaging and labeling of the product. For a variable period of time, a process unit actively manufactures a specific compound. At the end of the campaign for one product, another is scheduled to follow. After equipment cleaning, the same equipment is then used to make a completely different product, using different raw materials, executing a different recipe, and creating different wastes.

A variety of priority pollutants are used as reaction and purification solvents during chemical synthesis. According to the Detailed Questionnaire, priority pollutants used by facilities during the chemical synthesis process include benzene, chlorobenzene, chloroform, chloromethane, o-dichlorobenzene, 1,2-dichloroethane, methylene chloride, phenol, toluene, and cyanide.

The Detailed Questionnaire identified the top five nonconventional pollutants associated with chemical synthesis as methanol, acetone, isopropanol, ethyl acetate, and ethanol. Six-member ring compounds, such as xylene, pyridine, and toluene, are also widely used organic solvents because they are stable compounds that do not easily take part in chemical reactions. These compounds are used either in the manufacture of synthesized pharmaceuticals or are produced as the result of unwanted side reactions. Table 3-7 lists solvents used in chemical synthesis operations.

Solvents are used in chemical synthesis processes to dissolve gaseous, solid, or viscous reactants in order to bring all the reactants into close molecular proximity. Solvents also serve to transmit heat to or from the reacting molecules. By physically separating molecules from each other, solvents slow down some reactions that would otherwise take place too rapidly, resulting in unwanted side reactions and excessive temperature increases.

Some solvents are also used to control the reaction temperature. It is common practice in a batch-type synthesis to select a solvent which is compatible with the reaction and which has a boiling point the same as the desired reaction temperature. Heat is then applied to the reaction mass at a rate sufficient to keep the mixture boiling continuously. Vapors that rise from the reaction vessel are condensed, and the liquefied solvent is allowed to drain back into the reaction vessel. This refluxing prevents both overheating and overcooling of the reactor contents, and can automatically compensate for variations in the rate of release or absorption of chemical energy.

Many plants operate solvent recovery units that purify contaminated solvents for reuse. These units usually contain distillation columns, and may also include solvent/solvent extraction operations in which a second solvent is used to separate impurities. These operations may result in aqueous wastes that contain residues fully or partially saturated with residual solvent. Wastewater is generally produced with each chemical modification that requires filling and emptying the batch reactors. This wastewater can contain unreacted raw materials, as well as some solvents, along with a large number of compounds that differ due to the varied chemical reactions performed (e.g., nitration, amination, halogenation, sulfonation, alkylation). Chemical synthesis effluent generally has a high BOD_5 and COD waste load. The pollutants in chemical synthesis wastewater vary with respect to toxicity and biodegradability. The production steps may generate acids, bases, cyanides, metals, and other pollutants, while the waste process solutions and vessel wash water may contain residual organic solvents. Occasionally, chemical synthesis wastewater is incompatible with biological treatment systems because it is too concentrated or too toxic for the biomass in the treatment system. Thus, it may be necessary to equalize and/or chemically pretreat some chemical synthesis wastewater prior to biological treatment.

Primary sources of wastewater from chemical synthesis operations are: 1) process wastes such as spent solvents, filtrates, and concentrates; 2) floor and equipment wash water; 3) pump seal water; 4) wet scrubber wastewater; and 5) spills. Wastewater from chemical synthesis plants can be characterized as having high BOD_5, COD, and TSS concentrations; large flows; and extremely variable pH values, ranging from 1.0 to 11.0.

3.4.2.4 Mixing, Compounding, or Formulating

Pharmaceutically active ingredients are generally produced by batch processes in bulk form and must be converted to dosage form for consumer use. Common dosage forms for the consumer market are tablets, capsules, liquids, and ointments. In addition, active ingredients can also be incorporated into patches and time release capsules.

Tablets are formed in a tablet press machine by blending the active ingredient, filler, and binder. The filler (e.g., starch, sugar) is required to dilute the active medicinal ingredient to the proper concentration, and a binder (e.g., corn syrup or starch) is necessary to bind the tablet particles together. A lubricant (e.g., magnesium stearate) may be added for proper tablet machine operation. The dust generated during the mixing and tableting operation is collected and usually recycled directly to the same batch, while broken tablets generally are collected and recycled to the granulation operation in a subsequent lot. Some tablets are coated by tumbling with a coating material and then dried. After the tablets have been coated and dried, they are sent to the packaging unit where they are bottled. Tablet-coating operations can be a significant source of air emissions of solvents if solvent-based coatings are used, and can contribute solvents to the plant wastewater if certain types of air pollution control equipment (wet scrubbers or activated carbon) are used to capture solvent vapors from tablet-coating operations. Wastewater from the wet scrubber is likely to be sewered as is the condensate from the steam used to regenerate the activated carbon.

The first step in capsule production is to form a hard gelatine shell. The shells are produced by machines that dip rows of rounded metal dowels into a molten gelatine solution, and then strip the capsules from the dowels after the capsules have cooled and solidified. Imperfect capsules are remelted and reused, if possible, or sold for glue manufacture. Most pharmaceutical companies purchase empty capsules from a few specialty producers. The active ingredient and filler are mixed before being poured by machine into the empty gelatine capsules. The filled capsules are bottled and packaged. As in tablet production, some dust is generated, which is recycled to the production line. Liquid preparations are formulated for injection or oral use. In both cases, the liquid active ingredient is first weighed and then dissolved in water. Injectable solutions are bulk-sterilized by heat or filtration and then poured into sterilized bottles. Oral liquid preparations can be bottled directly without the sterilization steps. Wastewater is generated by general cleanup operations, spills, and breakage.

Ointments are produced by blending an active ingredient(s) with an ointment base such as polyethylene glycol. The blended product is then poured into tubes by machine and packaged. Wastewater generated from these operations are all from equipment cleaning operations.

The primary objective of mixing, compounding, or formulating operations is to convert the manufactured products into a final, usable form. The necessary production steps typically have small wastewater flows because very few of the unit operations generate wastewater. The primary use of water is in the actual formulating process, where it is used for cooling and for equipment and floor washing.

Wastewater sources from mixing, compounding, or formulating operations are: 1) floor and equipment wash water, 2) wet scrubbers, and 3) spills. The use of water to clean out mixing tanks can periodically flush dilute wastewaters of unusual composition into the plant sewer system. The washouts from mixing tanks may be used to prepare the master batches of the pharmaceutical compounds and may contain inorganic salts, sugars, and syrup. Other sources of contaminated wastewater are dust and fumes from scrubbers, either in building ventilation systems or on specific equipment. In general, this wastewater is readily treatable by biological treatment systems.

An analysis of the pollutant information in the pharmaceutical manufacturing database shows that wastewater from mixing, compounding, or formulating plants normally has low BOD_5, COD, and TSS concentrations; relatively small flows; and pH values of 6.0 to 8.0.

3.4.3 Pharmaceutical Manufacturing Process Variability

The wastewater effluent flow and composition from a typical pharmaceutical manufacturing facility can be highly variable. Factors contributing to such variability are:

- Campaigning;
- Batch processing; and
- Wastewater commingling.

Because many pharmaceutical products are manufactured in campaigns, most wastewater is generated during product changeover. The process equipment must be cleaned out to avoid product contamination. The composition of the wastewater will vary according to the products that were manufactured on that process line.

Pharmaceuticals are manufactured by batch and continuous manufacturing operations. Batch-type production is by far the most common manufacturing technique, as presented in the production operation breakdown in Table 3-8. Many pharmaceutical facilities conduct multiple batch operations, some in series and some concurrently. Often several of the required batch processes are performed at the same time in separate reactors, each with its own schedule. Each batch may have unique waste stream characteristics. In fermentation operations, it can take a few days to several weeks to complete the ferment, during which little or no wastewater is generated. However, during product recovery operations, high-volume, high-strength wastewaters are generated.

It is also common practice in the pharmaceutical manufacturing industry to commingle organic-contaminated wastewaters. In many cases commingling is necessary to collect sufficient wastewater volume to properly operate an economically sized treatment unit such as a steam stripper. Commingled wastes may be added to the treatment unit feed tank on a variable schedule, thus altering the feed composition on a real-time basis. In other cases, segregating for purposes of recovery and treatment may be appropriate and cost effective.

A variety of solvents are used in the pharmaceutical manufacturing industry and end up in the industry's wastewater. Many solvents are process-specific and cannot be interchanged in other pharmaceutical processes. In addition, solvents must be approved by the FDA for each process. FDA regulations require that before a change can be made to an approved process, industry must meet the requirements of product purity and product efficacy as specified in the FDA approval.

Consequently, simplification of wastestream composition by chemical substitution to a common solvent may not be possible or desirable. Nonetheless, EPA has worked with the Food and Drug Administration (FDA) to encourage pollution prevention in the final guidelines and standards. See 7.2.1.2 for a more detailed discussion of EPA and FDA efforts towards pollution prevention in the pharmaceutical industry.

3.5 Trends in the Industry

The "Preliminary Data Summary for the Pharmaceutical Point Source Category" (22) gives a snapshot of the pharmaceutical manufacturing industry in the late 1970s and the early 1980s. By comparing these pre-1986 sources to the data available in the 1989 Pharmaceutical Screener Questionnaire and the 1990 Detailed Questionnaire, trends in the manufacturing process types used by pharmaceutical manufacturing facilities, the treatment technologies used at pharmaceutical manufacturing facilities, and the chemicals used in their manufacturing processes were observed. These trends are described in the following subsections.

3.5.1 Manufacturing Process Types

Since 1986, the number of pharmaceutical manufacturing facilities engaging in fermentation has increased, while those engaging in biological or natural extraction has decreased. These trends are shown in the following table.

Type of Facility	Percentage of Facilities Using Process Prior to 1986	Percentage of Facilities Using Process in 1989/1990
Fermentation	7.8	14.5
Biological or Natural Extraction	17.0	14.5
Chemical Synthesis	29.3	30.3
Mixing, Compounding, or Formulating	80.0	80.0

The total of the percentages is not 100 because any one facility may manufacture multiple process types.

3.5.2 Treatment Technologies in Use

Table 3-9 presents the trends in wastewater treatment technologies used by pharmaceutical manufacturing facilities. Since 1986, the use of neutralization, equalization, activated sludge, primary clarification, multimedia filtration, steam stripping, secondary clarification, granular activated carbon, and oxidation have all increased, while the use of aerated lagoons, chlorination, waste stabilization ponds, and trickling filters has decreased slightly. Upward or downward trends cannot be assessed for settleable solids removal, primary sedimentation, polishing ponds, evaporation, dissolved air floatation, pH adjustment, or phase separation since data were not available for both pre-1986 and post-1986 time frames.

3.5.3 Chemical Substitution

The pharmaceutical manufacturing industry has decreased its use of many chemicals because of their toxicity and contribution to air and water pollution. Use of chlorinated compounds has decreased the most. Based on a review of TRI data from pharmaceutical manufacturing facilities, the average annual discharge of chloroform, methylene chloride, carbon tetrachloride, benzene, methyl isobutyl ketone, pyridine, phenol, methyl cellusolve, and xylene has decreased between the years 1987 and 1994. Percent reductions in annual discharge vary from 26% (phenol) to 99% (carbon tetrachloride). Table 3-10 presents the total annual discharge for 1987 and 1994, and the percent reductions for each compound.

Table 3-1

Facilities Sampled As Part of the Pharmaceutical Manufacturing Industry Study

Plant Code	Sampling Dates	Subcategory	Days Sampled	Stream Characterization	Technology Sampled			
					Biological	Steam Stripping	Resin Adsorption	Cyanide Destruction
1. Indirect Dischargers								
30618	04/19/86-04/21/86	A,B,C,D,E	2	X	--	--	--	--
30832	07/16/86-07/18/86	A,C,D,E	2	X	--	--	--	--
30759	07/29/86-07/31/86	A,B,C,D,E	2	X	X	--	--	--
30022	03/11/87-03/13/87	A,B,C,D,E	2	X	X	--	--	--
30918	05/10/88-05/12/88	A,B,C,E	2	X	--	--	--	--
30329	09/12/88-09/16/88	A,C,D,E	3	X	--	PC, FT, DP	--	--
30977	03/28/89-03/30/89	A,B,C,E	2	X	--	--	--	--
30618	06/05/89-06/09/89	A,B,C,D,E	4	--	--	PC	X	--
2. Direct Dischargers								
30010	02/25/87-02/27/87	C	2	X	X	--	--	--
30487	09/19/88-09/23/88	C	4	--	--	PC	--	--
30542	03/13/89-03/17/89	A,C,E	4	--	--	--	--	X
30623	04/03/90-04/13/90	A,C	10	X	X	--	--	--
30540	06/03/91-06/13/91	A,B,C,D,E	10	X	X	--	--	--

Notes: PC = packed column; FT = flash tank; DP = distillation pot.
Subcategory refers to the type of manufacturing operations performed at the facility.

Subcategory A = Fermentation
Subcategory B = Extraction
Subcategory C = Chemical Synthesis
Subcategory D = Formulation
Subcategory E = Research and Development

Table 3-2

Pharmaceutical Industry
Geographic Distribution(a)

Location	Number of Plants	Percentage of Total Plants	Total Number of Employees in Region
Eastern United States			
EPA Region I:			
Connecticut	7	2.3	
Maine	0	0.0	
Massachusetts	9	3.0	
New Hampshire	0	0.0	
Rhode Island	1	0.3	
Vermont	0	0.0	
EPA Region I Totals	17	5.6	7,025
EPA Region II			
New Jersey	46	15.1	
New York	28	9.2	
Puerto Rico	34	11.2	
Virgin Islands	0	0.0	
EPA Region II Totals	108	35.5	60,322
EPA Region III			
Delaware	2	0.7	
Maryland	3	1.0	
Pennsylvania	17	5.6	
Virginia	4	1.3	
West Virginia	1	0.3	
District of Columbia	0	0.0	
EPA Region III Totals	27	8.9	14,558

Table 3-2 (Continued)

Location	Number of Plants	Percentage of Total Plants	Total Number of Employees in Region
EPA Region IV			
Alabama	0	0.0	
Georgia	5	1.6	
Florida	2	0.7	
Mississippi	2	0.7	
North Carolina	11	3.6	
South Carolina	4	1.3	
Tennessee	7	2.3	
Kentucky	0	0.0	
EPA Region IV Totals	31	10.2	12,927
EPA Region V			
Illinois	14	4.6	
Indiana	12	4.0	
Ohio	11	3.6	
Michigan	9	3.0	
Wisconsin	2	0.7	
Minnesota	4	1.3	
EPA Region V Totals	52	17.1	37,235
Eastern U.S. Total (EPA Regions I-V)	**235**	**77.3**	**132,067**

Table 3-2 (Continued)

Location	Number of Plants	Percentage of Total Plants	Total Number of Employees in Region
Western United States			
EPA Region VI			
Arkansas	0	0.0	
Louisiana	3	1.0	
Oklahoma	0	0.0	
Texas	5	1.6	
New Mexico	0	0.0	
EPA Region VI Totals	8	2.6	2,121
EPA Region VII			
Iowa	4	1.3	
Kansas	5	1.6	
Missouri	17	5.6	
Nebraska	3	1.0	
EPA Region VII Totals	29	9.5	6,764
EPA Region VIII			
Colorado	4	1.3	
Utah	1	0.3	
Wyoming	1	0.3	
Montana	0	0.0	
North Dakota	0	0.0	
South Dakota	0	0.0	
EPA Region VIII Totals	6	2.0	1,252

Table 3-2 (Continued)

Location	Number of Plants	Percentage of Total Plants	Total Number of Employees in Region
EPA Region IX			
Arizona	1	0.3	
California	22	7.2	
Nevada	0	0.0	
Hawaii	0	0.0	
EPA Region IX Totals	23	7.6	9,520
EPA Region X			
Alaska	0	0.0	
Idaho	0	0.0	
Oregon	0	0.0	
Washington	3	1.0	
EPA Region X Totals	3	1.0	534
Western U.S. Total (EPA Regions VI-X)	**69**	**22.7**	**20,191**
U.S. Totals	**304**	**100**	**152,258**

(a) Employment obtained from the 1989 Screener Questionnaire. Facility locations obtained from the Detailed Questionnaire and the 1989 Screener Questionnaire.

Table 3-3

Distribution of Pharmaceutical Manufacturing Facilities by Date of Initiation of Operations(a)

Decade	Number of Facilities Reporting	
	Facility Operations Began	Pharmaceutical Manufacturing Operations Began
Prior to 1930s	19	10
1930s	6	5
1940s	14	14
1950s	17	18
1960s	26	27
1970s	47	46
1980s	50	57
1990s	4	5
No Response	61	62
Total	244	244

(a)Data obtained from 244 facilities responding to the Detailed Questionnaire.

Table 3-4

Example Pharmaceutical Products by Manufacturing Process and Classification

Fermentation Products	Extraction Products	Chemical Synthesis Products	Mixing/Compounding/ Formulating Products
Antibiotics Amphotericin Chlortetracycline Lincomycin Nystatin Penicillin G Penicillin V Streptomycin Vancomycin Antineoplastic Agents Dextran Therapeutic Nutrients Vitamins Ascorbic acid (C) Riboflavin (B2) Steroids	Antineoplastic Agents Vinblastine Vincristine Enzymes and Digestive Aids Pancreatin USP Papain Central Depressants Codeine Morphine Sulphate Noscapine Thebaine Hematological Agents Heparin Insulin Vaccines Strepvax II	Antibiotics Aztreonam Clindamycin Antihistamines Mecfizune dihydrochloride Cardiovascular Agents Methyldopa Central Stimulants Amitriptyline Caffeine Central Depressants Acetaminophen Aspirin (acetyl salicylic acid) Hormones Cortisone acetate Dexamethasone acetate Fluorometholone Hydrocortisone Testosterone Vitamins Niacinamide	Cold Formulas Benedryl elixir Dermatological Agents Calamine Salicylic acid Powders Desenex Powder Mouthwash Listerine Tablets and Capsules Contact Di-gel tablets Accutane Ointments Absorbine Jr. Lubriderm Caladryl Vicks Vaporrub

Table 3-5

Solvents Used in Fermentation Operations

Acetone	n-Heptane
Acetonitrile	n-Hexane
Ammonia (aqueous)	Isopropanol
n-Amyl acetate	Isopropyl acetate
Amyl alcohol	Methanol
n-Butyl acetate	Methyl cellosolve
n-Butyl alcohol	Methylene chloride
Chloroform	Methyl isobutyl ketone (MIBK)
N,N-Dimethylformamide	Petroleum naphtha
Ethanol	Phenol
Ethyl acetate	Toluene
Formaldehyde	Triethylamine

Table 3-6

Solvents Used in Biological or Natural Extraction Operations

Acetone	Ethylene glycol
Acetonitrile	Formaldehyde
Ammonia (aqueous)	n-Heptane
n-Amyl acetate	n-Hexane
Amyl alcohol	Isopropanol
n-Butyl alcohol	Isopropyl acetate
Chloroform	Isopropyl ether
1,2-Dichloroethane	Methanol
Diethylmine	Methylene chloride
Diethyl ether	Petroleum naphtha
N,N-Dimethylformamide	Phenol
Dimethyl sulfoxide	n-Propanol
1,4-Dioxane	Pyridine
Ethanol	Tetrahydrofuran
Ethyl acetate	Toluene

Table 3-7

Solvents Used in Chemical Synthesis Operations

Acetone	Formaldehyde
Acetonitrile	Formamide
Ammonia (aqueous)	Furfural
n-Amyl acetate	n-Heptane
Amyl alcohol	n-Hexane
Aniline	Isobutyraldehyde
Benzene	Isopropanol
2-Butanone (MEK)	Isopropyl acetate
n-Butyl acetate	Isopropyl ether
n-Butyl alcohol	Methanol
Chlorobenzene	Methylamine
Chloroform	Methyl cellosolve
Chloromethane	Methylene chloride
Cyclohexane	Methyl formate
o-Dichlorobenzene (1,2-Dichlorobenzene)	Methyl isobutyl ketone (MIBK)
1,2-Dichloroethane	2-Methylpyridine
Diethylamine	Petroleum naphtha
Diethyl Ether	Phenol
N,N-Dimethyl acetamide	Polyethylene glycol 600
Dimethylamine	n-Propanol
N,N-Dimethylaniline	Pyridine
N,N-Dimethylformamide	Tetrahydrofuran
Dimethyl sulfoxide	Toluene
1,4-Dioxane	Trichlorofluoromethane
Ethanol	Triethlyamine
Ethyl acetate	Xylenes
Ethylene glycol	

Table 3-8

Production Operation Breakdown(a)

Type of Operation	Number of Operations					Percent of Total Operation
	Manufacturing Processes				Total	
	Fermentation	Biological Extraction	Chemical Synthesis	Mixing/ Compounding/ Formulating		
Batch	309	189	1,059	3,675	5,232	99
Continuous	16	1	16	8	41	1
Total Number of Operations	325	190	1,075	3,683	5,273	100
Percent of Total Operations	6	4	20	70	100	
Percent of Subcategory Operations which are Batch	95	99	99	100	99	

(a) Production data obtained from 244 facilities responding to the Detailed Questionnaire.

Table 3-9

Trends in Treatment Technologies Used at Pharmaceutical Manufacturing Facilities(a)

Treatment Technology	Percentage of Facilities Using This Type of Treatment Technology Prior to 1986	Percentage of Facilities Using This Type of Treatment Technology in 1989/1990
Neutralization	26.0	44.3
Equalization	20.1	28.6
Activated sludge	16.9	20.5
Settleable solids removal	13.3	NA
Primary sedimentation	12.0	NA
Aerated lagoon	7.5	4.9
Primary clarification	3.9	9.8
Chlorination	3.6	2.5
Polishing ponds	3.2	NA
Waste stabilization pond	2.9	2.5
Trickling filter	2.9	2.0
Multimedia filtration	2.3	6.1
Steam stripping	1.9	5.7
Evaporation	1.9	NA
Secondary clarification	1.6	20.9
Granular activated carbon	1.3	3.3
Oxidation	1.0	2.0
Dissolved air flotation	1.0	NA
pH adjustment	NA	50.0
Phase separation	NA	12.3

The total of the percentages is not 100 because any one facility may have multiple treatment technologies and some facilities do not have treatment in place.

NA - Not available.

(a) Data obtained from reference 22 and the responses to the Detailed Questionnaire.

Table 3-10

Trends in Average Annual Discharges of Compounds Between the Years 1987 and 1994

Compound	Total Annual Discharge 1987 (lbs)	Total Annual Discharge 1994 (lbs)	Percent Change
Benzene	136,600	46,116	-66
Carbon tetrachloride	125,982	1,710	-99
Chloroform	664,456	336,587	-49
Methyl isobutyl ketone	2,918,922	960,365	-67
Methyl cellusolve	77,887	12,990	-83
Mehylene chloride	25,262,249	9,071,052	-64
Phenol	73,502	54,360	-26
Pyridine	216,100	75,280	-65
Xylene	1,469,212	492,394	-66

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